PANCREATIC HORMONES & ANTIDIABETIC DRUGS

I. THE ENDOCRINE PANCREAS

※ 胰島蘭氏小島　islet of Langerhans :

1.α cell :

(1) 分泌 Glucagon 升糖素

→促進肝糖分解 (glycoenolysis)

→升高血糖防止 hyopglycemia

(其分泌速率依血糖濃度而定)

即當血糖↓ → 升糖素 glucagin ↑)

(2) 亦分泌　Proglucagon

2.β cell :

分泌　insulin , c-peptide , proinsulin

3.δ cell

分泌　Somatostatin

4.F (pp cell) :

分泌　pancreatic polypeptide

Table 41-1.

TABLE 41–1 Pancreatic islet cells and their secretory products.

Cell Types	Approximate Percent of Islet Mass	Secretory Products
Alpha (A) cell	20	Glucagon, proglucagon
Beta (B) cell	75	Insulin, C-peptide, proinsulin, amylin
Delta (D) cell	3–5	Somatostatin
G cell	1	Gastrin
F cell (PP cell)[1]	1	Pancreatic polypeptide (PP)

[1]Within pancreatic polypeptide-rich lobules of adult islets, located only in the posterior portion of the head of the human pancreas, glucagon cells are scarce (< 0.5%) and F cells make up as much as 80% of the cells.

Diabetes Mellitus

1.1950 1.2 million USA

1975 5 million

1977 全世界 2 億人

1983 十大死因第八位

1985 十大死因第七位

2.DM is a disorder of carbohydrate 、 protein & lipid metabolism.

TypeⅠ Juvenile 幼年 →用 insulin IDDM

TypeⅡ Maturity 成年 →用口服 NIDDM

Diabetes Mellitus

- Epinephrine 會引起 hepatic glycogenolysis

  ∴產生 yransient hyoerglycemia
- 使用過量 Steroid → DM ，叫做 Steroid diabetes
- 甲狀腺中毒 (Thyrotoxicosis) 會增加血中 glucose level ↑
- Stress, 增加 insulin 需要↑

(1).DM 由於 Carbohydrate metabolism ↓

Protein lipid metabolism↑

(a)如 glucose 從 body store 中流出

因其 metabolism ↓ ，不能有效利用，積聚於血中，即成血糖↑

(b) 血糖↑

通過絲球體 glomeruli ， 濾出大量之葡萄糖

因超過近端腎小管之在吸收能力，即無法再吸收 glucose

∴glucose 出現在尿 (glucosuria)

(2).

Aldise reductase

組織內之 glucose ——→ sorbitol

——→

NAD-sorbitol or 2- Dehydrogenase

Fructose

(減低代謝)

∵其 metbolism ↓

∴Sorbitol 留在 cell 內，引起白內障 (Cataract) → retinopathy 視網膜病

又 Sorbitol 聚集於末梢神經→神經麻木。

(3).Protein metabolism ↑

Nitrogen 排泄 ↑

lipid ， FA 之代謝↑

其代謝物叫做 ketone body

(如 acetoacetic acid ， β –hydroxybutyric acid , acetine…..)

∴ ketoacidosis → coma →death

總之 DM ，由於大量 glucose 帶著水、 Nitrogenous substance 、 ketone body → 由 glomerylar 排出。

∴電解質排出，失水、餓、渴。

Type1 ， Insulin 低，若不補充 Insulin 則會發生 metablic acidosis (Ketosis) → 昏迷，死亡。

- Diabetic ketoacidosis
- Ketone body 在 liver 由 acetyl CoA 合成而來是放入血中→ 心、骨髓肌拿當作能量來源。在延遲飲食下， ketone body 濃度很低。
- 另 Insulin 抑制 lipolysis (減少 fatty acid supply) 而 fatty acid 先 acetyl CoA 在肝臟中之主要來源。
- 以 Ketone 指稱 ketosis 是不太適合的，因 Detine body 是 β-hydroxy-butyrate
- 糖尿病人所製造之 ketone body 除了 acetone 外，其餘都是有機酸 (Ketone body 過多而導致變酸)
- 另 acetone 是 volatile ，可經由肺排出。

∴ 嚴重 ketone body 過多病人有 acetone breath (丙酮味)

2.Non-Insulin-dependent DM（NIDDM）Type 2

- 通常發生在 35 歲以上，肥胖者
- 與 Type 1 比較 ：TypeⅡ 病人血中有相當之 Insulin
- 少量 Insulin 即可抑制 ketone body 的產生。∴很少產生 ketone body 過多的現象。

- Type 2 有些人 Insulin 雖然很高，但仍有高血糖，因對 Insulin 之 target cell 產生 insensitive 。
- 這能有 Insulin 抵抗性的細胞，需要有更高之 Insulin 濃度才能使其產生反應。
- 有些病人因細胞上 Insulin receptor 數量減少
- 因 Type 2 病患有內生性胰島素，可以避免酮體過多，也很少發生昏迷，但會發生高滲透性昏迷 (hyperosmolar coma) ，此現象常發生老人，生病後或刺激後，導致胰島素需求增加所起，胰島素相對地缺乏，造成尿糖，若病人有其他疾病如嘔吐，就更加重失水。

失水嚴重→尿量會漸減少，→糖就無法由尿排出→血糖及血漿滲透度上升→意識喪失。

3.Type 3 Diabetes Mellitus :

因胰臟切除、胰臟炎、 nonpancreatic disease 藥物治療等使血糖↑。

4.Type 4 DM :

- 妊娠糖尿病 Gestational diabetes (GDM) 當第 1 次懷孕、血糖不正常上升。
- 於懷孕末三個月 (last trimester) ，胎盤及胎盤 hormones 會產生 insulin resistance.
- ∴第一次產前檢查 (prenatal visit) 要做 diabetes 檢查。

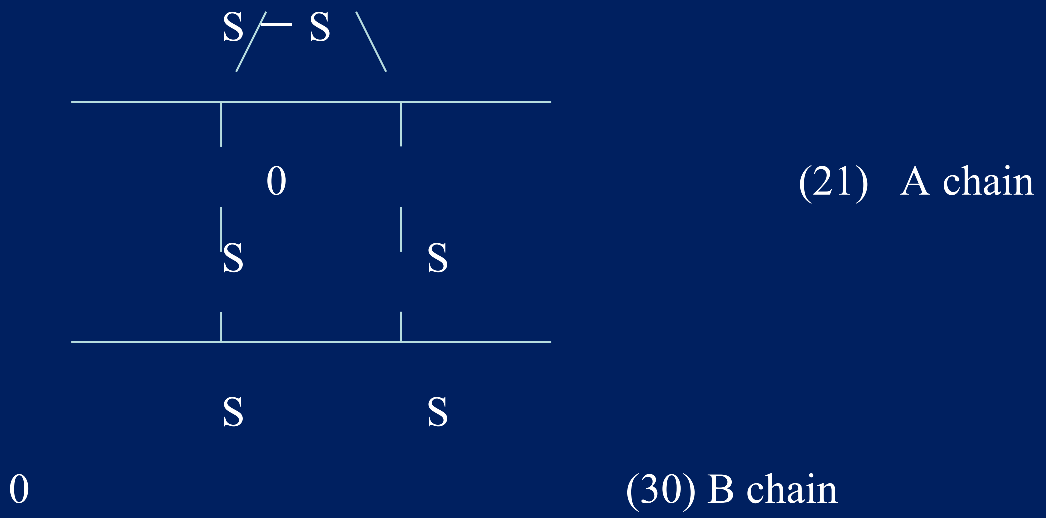
Ⅱ.INSULIN

- Chemistry

  有 51 amino acid

  分由二個 pokypeptide chain 並由 disulfide 連接

Mol. W’t =5,808



Ⅱ. INSULIN

- 不同物種 (species) 之胰島素，其胺基酸排列相當類似，牛的胰島素與人有三個氨基酸不同，株的胰島素與人有一個氨基酸不同∴ (豬的胰島素在人體有較低之抗原性)
- Insulin 刺激 glucose 進入 muscle and fat cell (Insulin 並不進入細胞內，而與細胞表面 receptor 結合，促使反應進行)

◆Inslin Secretion

1. release from : pancreatic 胰臟的 B cell

2.Stimulants : glucose 、 sugars (eg. Mannose)

certain amino acid (eg. Leucine , arginine)

vagal activity 迷走神經

3.Hyperglycemia 高血糖

→↑細胞內 ATP levels

→close ATP-dependent potassium channels K+

→↓outward potassium current through channel

→B cell depolarization

→open voltage-gated calcium channels Ca^{++}

→細胞內由鈣離子誘發分泌之 hormone ↑

Figure 41–2.

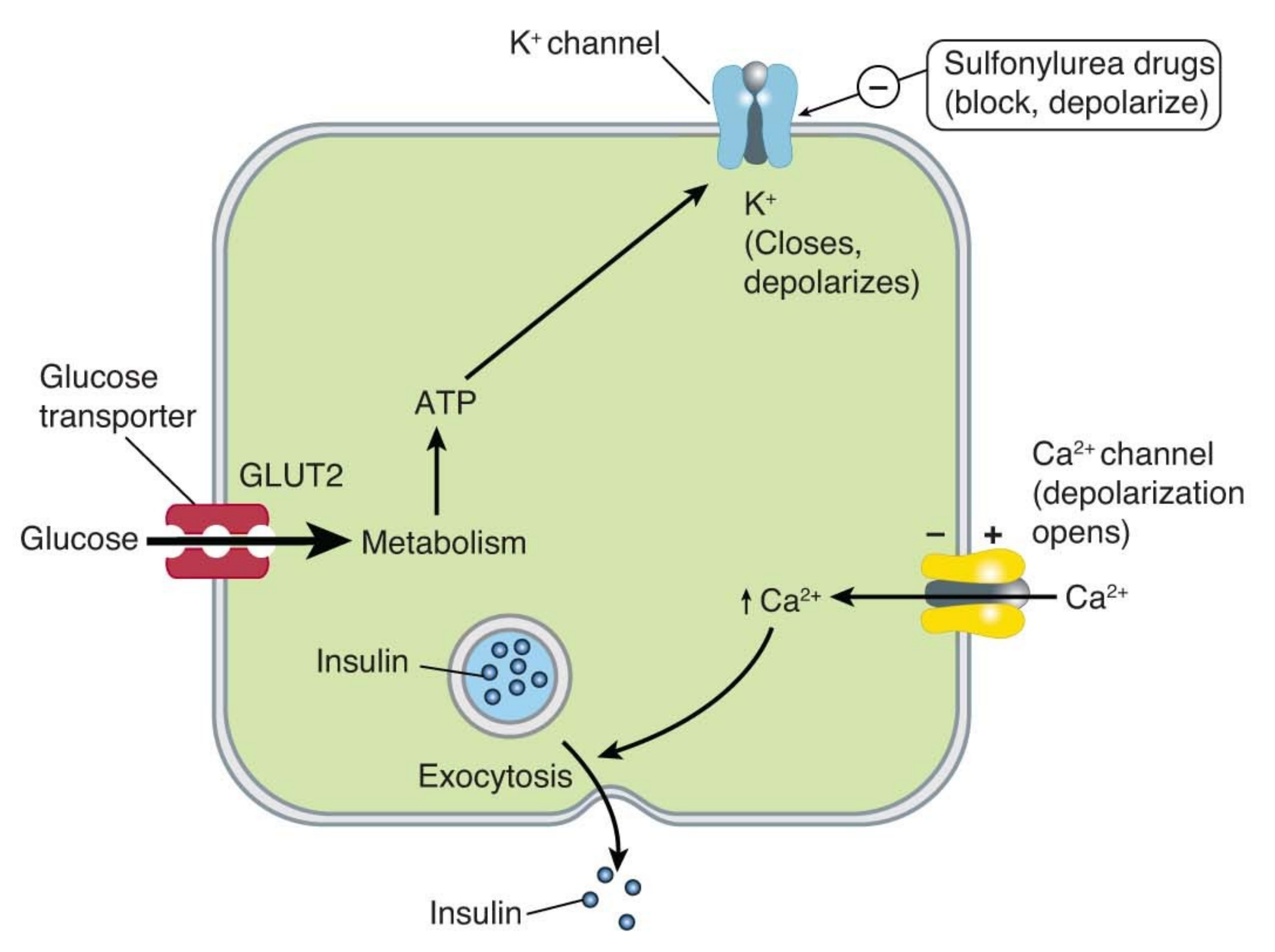


FIGURE 41–2 One model of control of insulin release from the pancreatic beta cell by glucose and by sulfonylurea drugs. In the resting cell with normal (low) ATP levels, potassium diffuses down its concentration gradient through ATP-gated potassium channels, maintaining the intracellular potential at a fully polarized, negative level. Insulin release is minimal. If glucose concentration rises, ATP production increases, potassium channels close, and depolarization of the cell results. As in muscle and nerve, voltage-gated calcium channels open in response to depolarization, allowing more calcium to enter the cell. Increased intracellular calcium results in increased insulin secretion. Insulin secretagogues close the ATP-dependent potassium channel, thereby depolarizing the membrane and causing increased insulin release by the same mechanism. (Modified and reproduced, with permission, from *Basic & Clinical Endocrinology*, 4th ed. Greenspan F, Baxter JD [editors]: Originally published by Appleton & Lange. Copyright © 1994 by The McGraw-Hill Companies, Inc.)

◆Insuline Degradation

- A chain 及 B chain 由 disulfide 連接
- 受 glutathione insulin transhydrogenase (insulinase) 所分解→ 60% 由肝， 40% 由腎代謝
- $t_{½}$=3-5 分

◆Measurement of Circulating Insuline

*radioimmunoassay

*In normal humane

basal insulin values =5-15 μU/mL(30-90 pmol/L)

meal peak rise 60-90 μU/mL (360-540 pmol/L) (用餐後之高峰)

◆The Insuline Receptor

- Insuline 第一步必須與 insulin receptor 結合，才能有信號傳遞
- 胰島素接受體是一個 tetrameric protein complex
- 含有二個 α 分子，分子量 130,000 dalton 及二個 β 分子，分子量 9000 dalton
- 最近發現 insulin receptor 本身是一個 protein tyrosine kinase
- Insulin 與 receptor 上的 α- subunit 結合，再活化 β – subunit 上之 kunase

Figure 41–3.

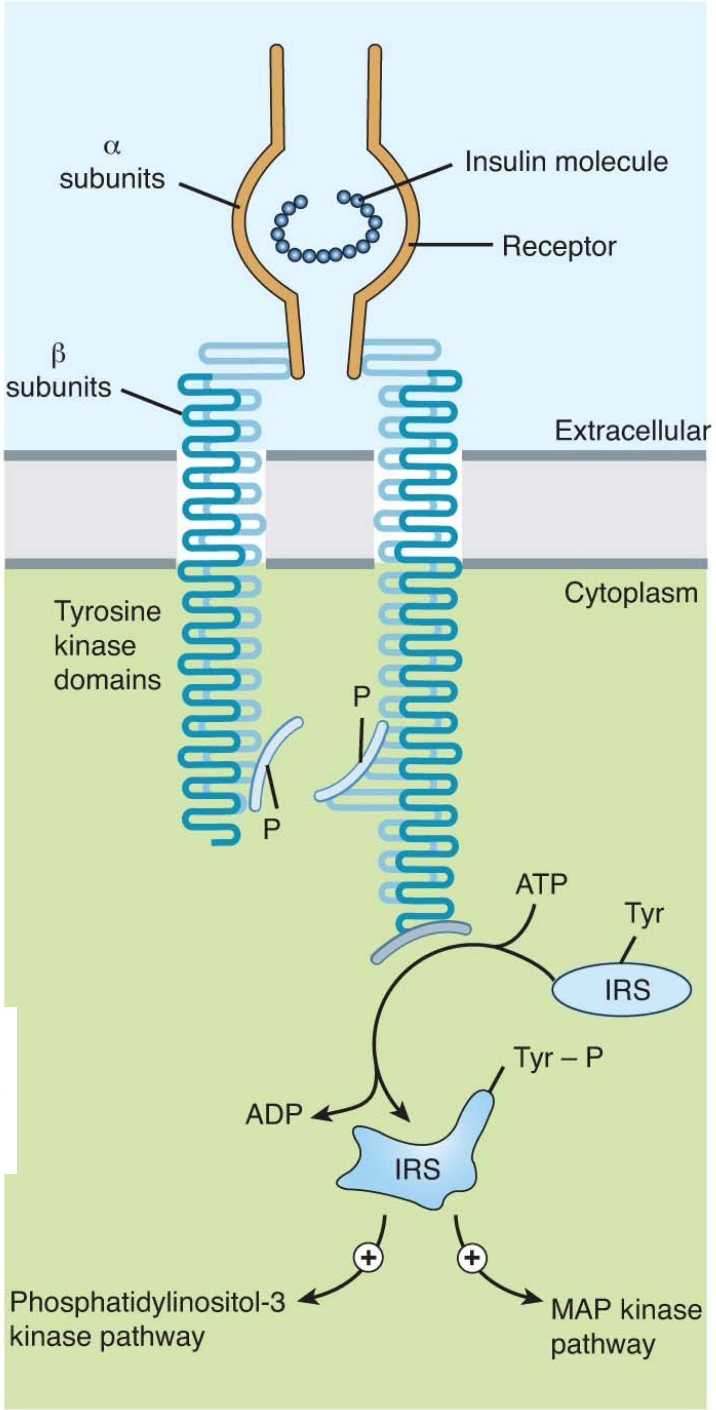


FIGURE 41–3 Schematic diagram of the insulin receptor heterodimer in the activated state. IRS, insulin receptor substrate; MAP, mitogen-activated protein; P, phosphate; tyr, tyrosine.

- Glucose transporters (葡萄糖轉運者)

→幫助 glucose uptake 進入細胞膜內

→Glucose transporter 4(GLUT 4) 主要是位於骨骼肌細胞負責運輸葡萄糖的功能。

→糖尿病患者， GLUT 4 會降低

→GLUT 1,2,3,4,5

Table 41-2.

TABLE 41–2 Glucose transporters.

Transporter	Tissues	Glucose K_m (mmol/L)	Function
GLUT 1	All tissues, especially red cells, brain	1–2	Basal uptake of glucose; transport across the blood-brain barrier
GLUT 2	Beta cells of pancreas; liver, kidney; gut	15–20	Regulation of insulin release, other aspects of glucose homeostasis
GLUT 3	Brain, kidney, placenta, other tissues	< 1	Uptake into neurons, other tissues
GLUT 4	Muscle, adipose	≈ 5	Insulin-mediated uptake of glucose
GLUT 5	Gut, kidney	1–2	Absorption of fructose

GLUT 4

葡萄糖轉運子 4(glucose transporter 4 , GLUT 4) 主要位於骨骼肌細胞負責運輸葡萄糖，是骨骼肌數種葡萄糖運輸蛋白異構體 (isoform) 中， 表現量最多的蛋白。

GLUT4 蛋白存於細胞內，當胰島素濃度增加或肌肉收縮時，才會由細胞內移之細胞膜表面，發揮運輸葡萄糖的功能。運輸到細胞內的葡萄糖可提供能量代謝或肝醣合成，所以 GLUT4 為肌肉中肝醣在合成作用的重要因子。

圖一 : 肝醣合成是骨骼肌肝醣合成的最後一個步驟也是其限制步驟 (Lawrence &Roach ,1997)。

GLUT 4

肌肉中的肝醣合成首先要將葡萄糖轉運到細胞內，這個步驟是由葡萄糖轉運體 (Glucose transporter) 所控制，稱之為 GLUT4 。葡萄糖進入肌肉細胞後，馬上被 Hexokinase (HK) 磷酸化形成 Glucose 6-phosphate (G 6-P) ，最後肝醣合成酶利用 UDT-glucose (UDPG) 來合成肌肉肝醣。 GLUT4 一般是位於細胞膜內，經胰島素刺激後 GLUT4 會轉移 (translocation) 到細胞膜表面來幫助葡萄糖進入細胞內 (這個步驟也被認為是肝醣合成的一個限制步驟) (Shulman,2000) 。

Lawrence, J.C.,& Roach,P.J.(1997) . NEW insights into the role and mechanism of glycogen synthase activation by insulin. Diabetes ,46 (4) , 541-547.

Shulman,G.I.(2000) . cellular mechanisms of insulin resistance .J.Clin .Inves,106(2) , 171-176

Figure 41–4.

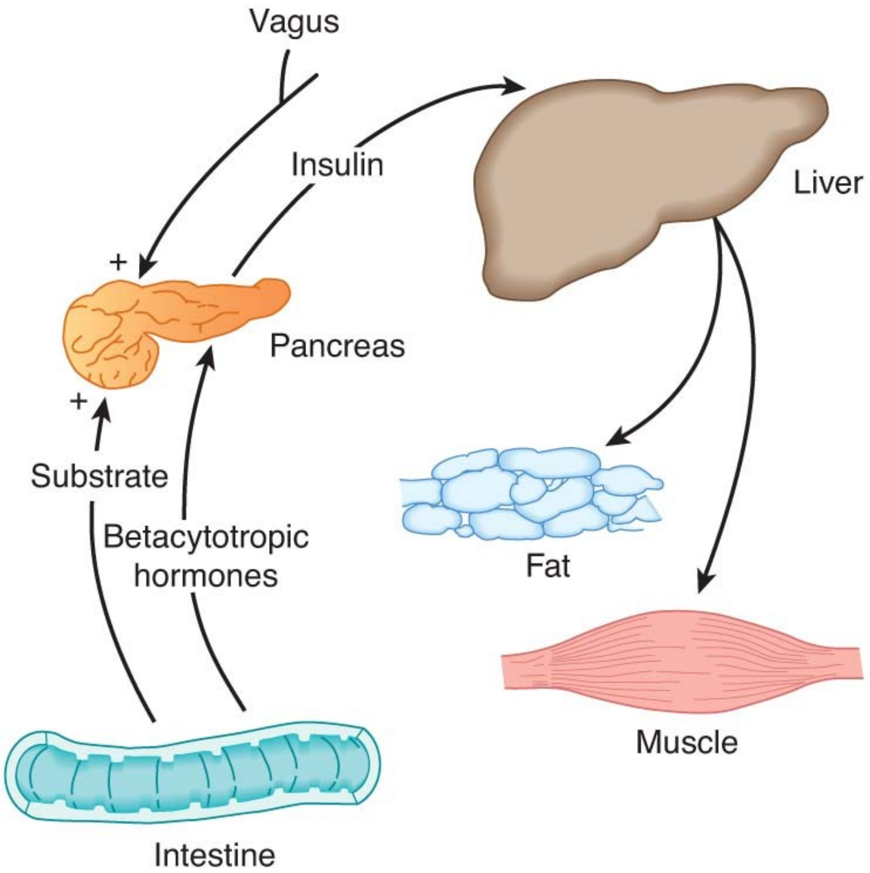
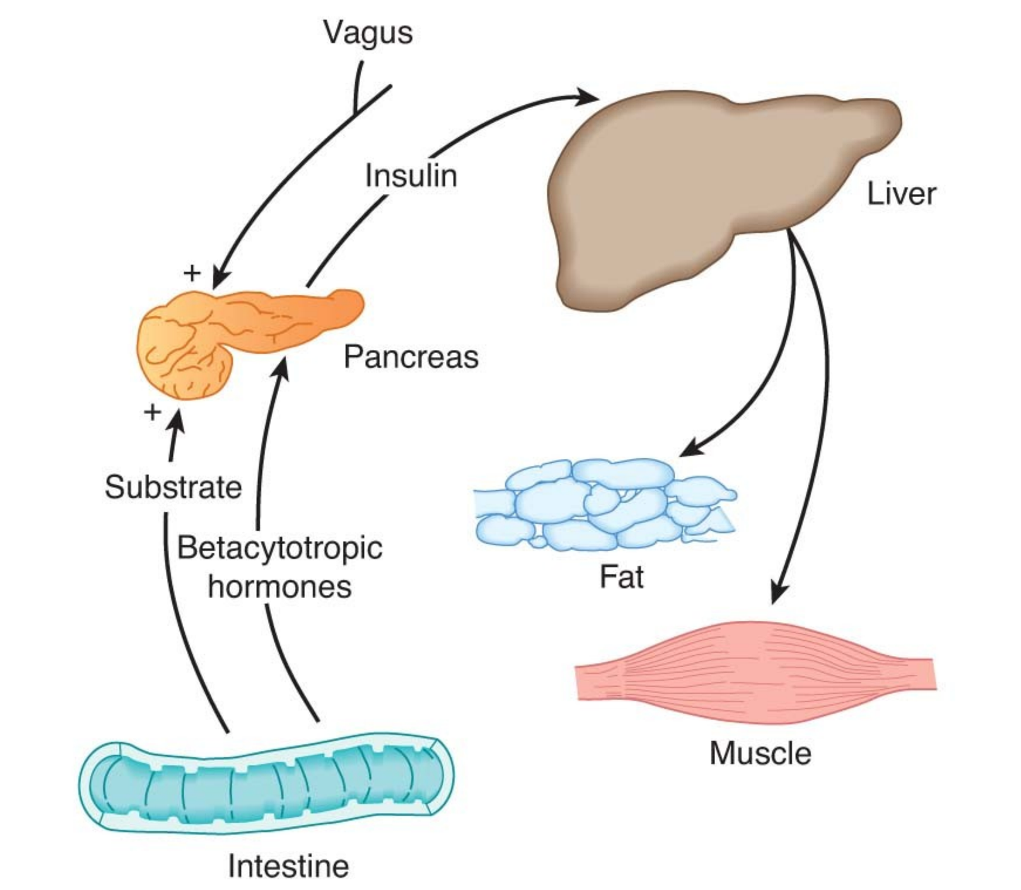


FIGURE 41–4 Insulin promotes synthesis (from circulating nutrients) and storage of glycogen, triglycerides, and protein in its major target tissues: liver, fat, and muscle. The release of insulin from the pancreas is stimulated by increased blood glucose, incretins, vagal nerve stimulation, and other factors (see text).

◆Effects of Insulin on Its Targets

- Insulin 促進 fat 及 glucose(energy 來源) 儲存在 target cell.
- 影響不同組織之細胞成長及代謝



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A. Action of Insulin on Liver

(I)Insulin 抑制 glycogenolysis (糖質分解)

∴促進 glucose 以 glucogen 貯存在於肝臟

(Ⅱ) Insulin 減少 Gluconeogenesis (葡萄糖新生)

由 noncarbohydrate substance

↓conversion into

glucose ⟶ 叫做葡萄糖新生

∵Insulin 減少循環中

gluconeogenic substrate (glycerol)

∴glucerol ↓ ⟶ glucose↓

B.On Muscle

- Insulin 增加蛋白質合成
- 另由於 muscle activity 消耗 glycogen stores

∴促進 glycogen synthesis

同時增加 glucose 進入 muscle cell↑

C.On Adipose Tissue :

Insulin 為 potent antilipoly agent

及減少脂肪組織之脂解作用，

∴減少循環 FFA ，促進 TG 貯存於脂肪細胞。

Table 41-3.

TABLE 41–3 Endocrine effects of insulin.

Effect on liver:
Reversal of catabolic features of insulin deficiency
Inhibits glycogenolysis
Inhibits conversion of fatty acids and amino acids to keto acids
Inhibits conversion of amino acids to glucose
Anabolic action
Promotes glucose storage as glycogen (induces glucokinase and glycogen synthase, inhibits phosphorylase)
Increases triglyceride synthesis and very-low-density lipoprotein formation
Effect on muscle:
Increased protein synthesis
Increases amino acid transport
Increases ribosomal protein synthesis
Increased glycogen synthesis
Increases glucose transport
Induces glycogen synthase and inhibits phosphorylase
Effect on adipose tissue:
Increased triglyceride storage
Lipoprotein lipase is induced and activated by insulin to hydrolyze triglycerides from lipoproteins
Glucose transport into cell provides glycerol phosphate to permit esterification of fatty acids supplied by lipoprotein transport
Intracellular lipase is inhibited by insulin

◆Characteristice of Available Insulin Preparations

＊製劑要注射給藥，因口服時對胃腸道破壞，除急救外大部分 S.C

A.Principal Tupes and Duration of Action of Insulin Preparation

1.Short-acting insulin

＊ Regular insulin

→ short-acting solube crystalline zinc insuline

→onset :15 min s.c.

→duration :5-7hrs

→為一可 i.v. or infusion pumps 之 insulin

→→

2.Lente and ultualente insulin(premixed insulins)

(1).Lente insulin = 30% semilente +70% ultralente insulin

*semilent : insulin with zinc ions 溶於 acetate buffer onset 快

*ultrakente insulin : poorly solube crystal of zinc insuline

(2) 主要與一些長效型胰島素混合使用

以得到一個快速升高之 insulin 血中濃度效果吸收快作用強

(3)Ultralente

→sliw onset &prolonged duration

→once or twice / day

3.NPH(neutral protamine Hagedorn , or isopgane) insulin

→N：代表中性　neutral

P：代表含有　protamine

H：代表丹麥科學家　Hagedorn 所發展

→混合時若於經蛋白之含量過高會與剛加入之胰島素形成顆粒沉澱下來

→NPH：只含低濃度為結合泰於精蛋白之製劑

0.3-0.4 mg protamine +4 mg insulin (100 IU)

→Nature protamine hagedorn

onset : 3-4 hrs; duratuin :36 hrs

4.Long-acting insulins

Insulin detemir

Figure 41–5.

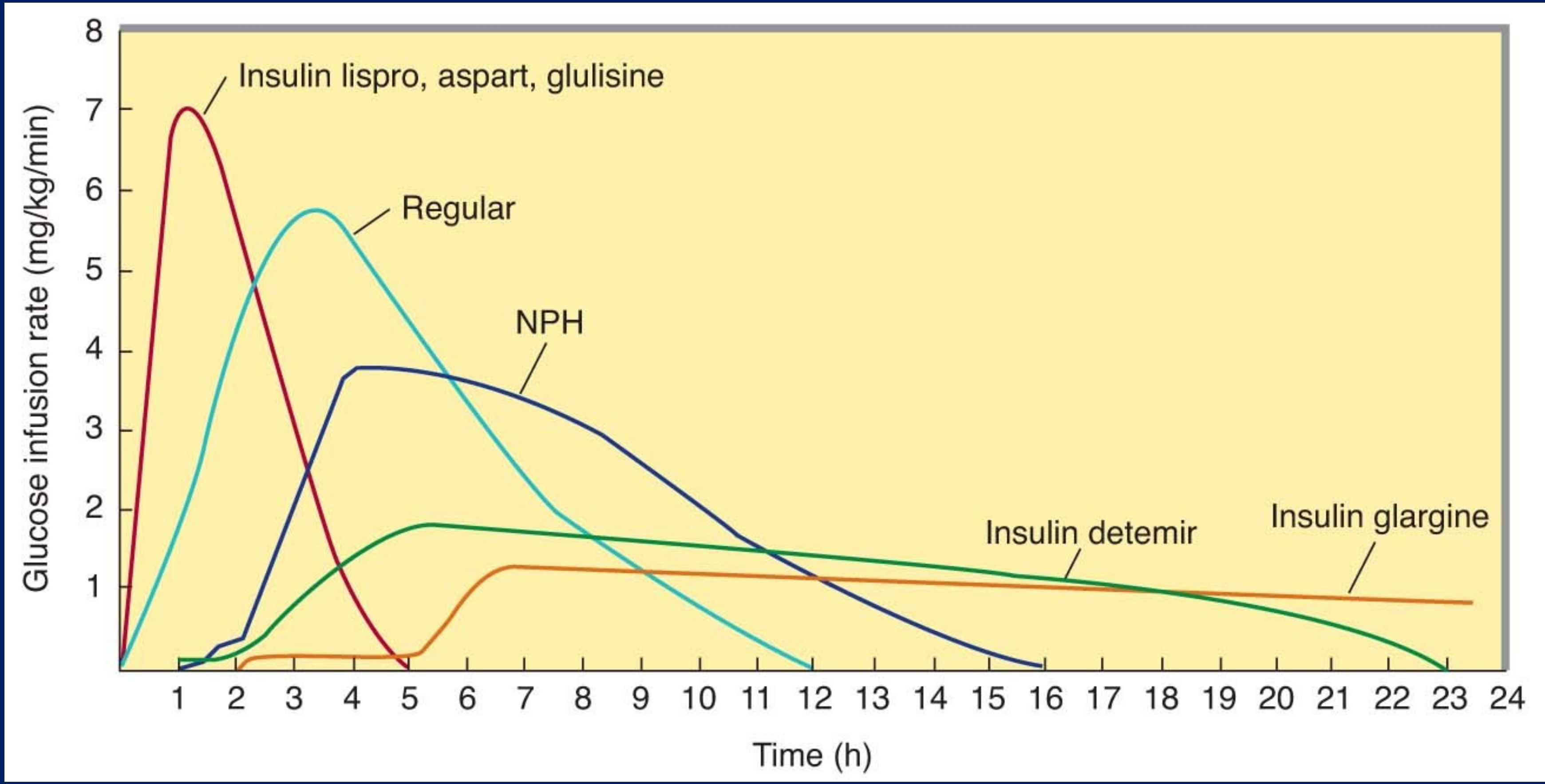

FIGURE 41–5 Extent and duration of action of various types of insulin as indicated by the glucose infusion rates (mg/kg/min) required to maintain a constant glucose concentration. The durations of action shown are typical of an average dose of 0.2–0.3 U/kg. The durations of regular and NPH insulin increase considerably when dosage is increased.

Table 41-4.

TABLE 41–4 Some insulin preparations available in the USA.[1]

Preparation	Species Source	Concentration
Rapid-acting insulins		
Insulin Lispro, Humalog (Lilly)	Human analog	U100
Insulin Aspart, Novolog (Novo Nordisk)	Human analog	U100
Insulin Glulisine, Apidra (Aventis)	Human analog	U100
Short-acting insulins		
Regular Novolin R (Novo Nordisk)	Human	U100
Regular Humulin R (Lilly)	Human	U100, U500
Intermediate-acting insulins		
NPH Humulin N (Lilly)	Human	U100
NPH Novolin N (Novo Nordisk)	Human	U100
Premixed insulins		
Novolin 70 NPH/30 regular (Novo Nordisk)	Human	U100
Humulin 70 NPH/30 regular and 50/50 (Lilly)	Human	U100
50/50 NPL, Lispro (Lilly)	Human analog	U100
75/25 NPL, Lispro (Lilly)	Human analog	U100
70/30 NPA, Aspart (Novo Nordisk)	Human analog	U100
Long-acting insulins		
Insulin detemir, Levemir (Novo Nordisk)	Human analog	U100
Insulin glargine, Lantus (Aventis/Hoechst Marion Roussel)	Human analog	U100

[1]These agents (except insulin lispro, insulin aspart, insulin detemir, insulin glulisine, and U500 regular Humulin) are available without a prescription. All insuli refrigerated and brought to room temperature just before injection.

NPL, neutral protamine lispro; NPA, neutral protamine aspart.

B.Species of Insulin

1.Beef /pork insulin

USA standard mixtures :70%beef+30%pork insulin

Novolin : 人工合成

利用豬之 insulin 改變

2.Human insulin

→利用 E coli or yeast 進行 DHA 重組而製造

→ 70% NPH +30%regular human insulin

可用於年紀較大或其他 insulin 製劑應用困難之患者

→由人體 proinsulin 基因合成

→Humulin

C .Concentration

USA 100IU /Ml(U100)

◆Complications of Insulin Therapy 併發症

1. Hypoglycemia:

CNS : mental confusion , bizarre behavior, coma .

Autonmic hyperactivity : tachycardia, palpitation ,sweating , tremor.

parasympathetic ： nausea , hunger .

趕快給 glucose

20-50ml 50% glucose I.V. 點滴 2-3 分內打完

2.Immunopathology of Insulin Therapy

a. Insulin Allergy

發生 urticaria，由於 anti-insulin IgE antibody

使 mast cell 釋放出 histamine

b. Immume Insulin Resisance

IgG –anti-insulin antibody 中和 insulin 作用

3.Lipodystrophy at injection sites (脂肪萎縮)

insulin lipoma 發生於注射部位

Ⅲ.ORAL HYPOGLYCEMIC AGENTS

1.Sulfonylures (第一代藥)

1955 年使於 NIDD

【機轉】 :

直接刺激蘭氏小島 Pancreatic β cell 分泌 insulin ，

增加血中 insulin level ↑

減低血中 glucgon level ↓

長期服用，能減少 glucose 從 liver outflow 出來。

增強 insulin 與 receptor binding

對於嚴重及幼年型無效。

Ⅲ.Oral Antidiabetic Agents

一 . 胰島素促泌素

Insulin Secretagogues

1.Sulfonylureas

Mechanism of Action

直接刺激蘭氏小島 pancveatic β cell 分泌 insulin.

其機轉是 :

→減少血中 glucagon level ↓

→關閉 potassium channel (extrapancreatic tissue)

Ⅲ.Oral Antidiabetic Agents

一 . 胰島素促泌素

A. Insulin release from pancreatic Beta Cells:

→Sulfonylurea 結合 beta-cell 之 ATP-sensitive potassiam channel 關閉鉀離子流出。

→經由細胞去極化

→打開 calcium channel 鈣流入

→insulin release

Ⅲ.Oral Antidiabetic Agents

一 . 胰島素促泌素

B. Reduction of serum glucagon concent ration

→長期給予 type 2 diabetics

sulfonylurea 可減少血中 glucagon level↓

p.738 table 41-5

※Efficacy and safety of the sultonylureas

- 1984 年 FDA 命令所有 sultonylureas 應加警語 : 可能增加因於心血管疾病而死亡之危險性

※ 第一代 :Tolbutamide ,Chlorpropamide ,Tolzamide .

第二代 :Glyburide ,Glipizide , Glimepiride

Table 41-5.

TABLE 41–5 Regulation of insulin release in humans.

Stimulants of insulin release
Glucose, mannose
Leucine
Vagal stimulation
Sulfonylureas
Amplifiers of glucose-induced insulin release
Hormones:
Glucagon-like peptide 1(7–37)
Gastrin inhibitory peptide
Cholecystokinin
Secretin, gastrin, glucagon
Neural amplifiers:
β-Adrenoceptor stimulation
Amino acids:
Arginine
Inhibitors of insulin release
Neural: α-Sympathomimetic effect of catecholamines
Humoral: Somatostatin, leptin
Drugs: Diazoxide, phenytoin, vinblastine, colchicine

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(1)First – Generation sulfonylureas

①Tolbutamide (Orinase): 吸收佳，快速在肝中代謝、半衰期 4-5hr 、 500mg 分次給予 (飯前，睡前)

②chlorpropamide (Diabinese): 半衰期 32hr，一天一次 (每天 250mg) 、經由肝代謝、本品與依賴 hepatic oxidative catablism 之藥物有相互作用、∴對肝腎機能不全之病人是禁忌 (contraindication)

③Tolazamide (Tolinase) : 半衰期 7hr. 、吸收慢。

(2) Second-Generation Sulfonylureas

- 副作用及 drug interaction 較少
- 但對心血管疾病及老年病人應注意會很危險地發生 hypoglycemia

①Glyburide (Diabeta): 每天開使用量 2.5mg/d 或更少、平均維持是 5-10mg/day , 早上給予

②Glipizide (Glucotrol): 半衰期短 2-4hr 、 常用量 5mg/day

③Glimepiride (Amaryl): 每天一次、對於不能以飲食或運動控制血糖濃度之病人， 本品與 insulin 合併使用以降血糖。

Sulfonylureas 藥品

【 Pharmacokinetic 】

- 大部分 sulfonylurease 在消化道很快被完全吸收並且在血漿中與血漿蛋白結合。
- 在肝臟被代謝，由腎排泄
- Tolbutamide 的半衰期最短，而且很快被代謝，失去活性
- Tolbutamide : 吸收最慢，代謝物稍具降血糖作用，但排泄很快。
- Chlorpropamide 有最長的半衰期 (一天用一次)
- 所有 Sulfonylureas 很容易與 plasma protein 結合，但第一代藥物的結合會被其他與離子結合之藥物所取代，而第二代藥物不會被取代 (因已非離子鍵與白蛋白結合)

Sulfonylureas 藥品

【副作用】：

肌肉無力、 ataxia , confusion ,skin rash , blood dyscrasias , jaundice.

【相互作用】 ：

a. 不能與 thiazide 配合→加重 DM.

b. 減低酒精耐量 .

c. 增加本品作用者 :β-blocker , Aspirin

【註】 :Sulfonylurea 之 降血糖作用 (及增加 insulin 敏感度 , 及其分泌) 雖被懷疑 . 但此作用必須有 insulin 存在 (無論在血液或 β cell) 才有作用 . 因此 sulfonylea 對 Type1 無效。

2.Repaglinde (Prandin) : Meglitinide 類

- 新第一類胰島素促泌素 , 1998 年 FDA 核准上市
- 作用機轉是調整 K 離子通道→ insulin 分泌
- 本品 onset 快 , duration of action 5-8 hr
- 可使用於飯後控制短程血糖
- 飯前 0.25-4mg
- 若用餐延遲→會發生 hypoglycemia
- 肝，腎功能不全者應小心使用

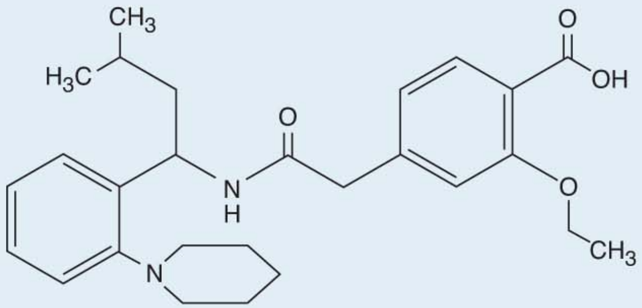
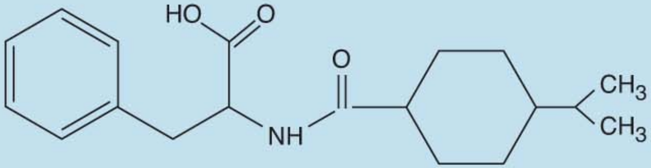
3.Nateglinide : D- phenylalanine derivative

- 快速刺激及短暫從 beta cell → 分泌 insulin (經由關閉 ATP-sensitive K^+ channel)

p740.Tab 41-7

Table 41-7.

TABLE 41–7 Other insulin secretagogues.

Drug	Chemical Structure	Oral Dose	$t_{1/2}$	Duration of Action (hours)
Repaglinide (Prandin)		0.25–4 mg before meals	1 hour	4–5
Nateglinide (Starlix)		60–120 mg before meals	1 hour	4

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二、 Biguanides (Metforlmin)

【機轉】：

(1) 直接刺激末梢組織 glycolysis ，∴增加 glucose 從血中去除

(2) 減少肝中 gluconeogenesis ↓

(3) 減慢 glucose 從 GI 吸收↓

(4) 減少血中 glucagon level ↓

(5) 增加 insulin binding to insulin receptor ↑

※因本品引起組織缺氧，使體內之葡萄糖在缺氧下，糖分解袋謝進行

∴Pyruvic acid , citric acid 及 lactic acid 均↑

→ lactic acidosis (死亡率 50%)

構造式 p.741

三、 Thiazolidinediones (Tzds)

◎本類藥品能降低 insulin resistance↓

◎與 peroxisome proliferator-activated receptor –gamma (PPAR-r) 在特定位置配對

- 影響 lipid 與 glucose 代謝 ,insulin 基因轉錄，脂肪細胞及其他組織之分化。
- 本品經由增加肌肉與脂肪組織的 glucose 回收與代謝→減少 insulin resistance

1.pioglitazone (Actos)

– 服用後 2hr 吸收

∴食物延遲攝食，不影響其 bioavailability .

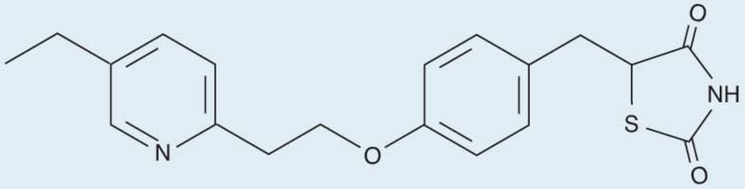
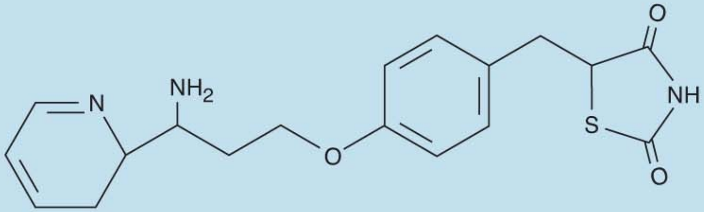
2.Rosiglitazone (Avandia)

◎快速吸收

◎每天 1~2 次 (4~8mg)

Table 41-8.

TABLE 41–8 Thiazolidinediones.

Thiazolidinedione	Chemical Structure	Oral Dose
Pioglitazone (Actos)		15–45 mg once daily
Rosiglitazone (Avandia)		2–8 mg once daily

四、 Alpha-Glucoseidase inhibitors

◎只有單醣類 (glucose) 可從腸道→ 進入血流。

◎複雜的澱粉雙醣類 (disaccharide) 消化過程必須 α amylase 或 α hlucosidase 所以裂解

→變成單醣分子，才能被腸道吸收。

◎Acarbose 與 miglitol 是小腸 α-glucosidase 競爭抑制劑，

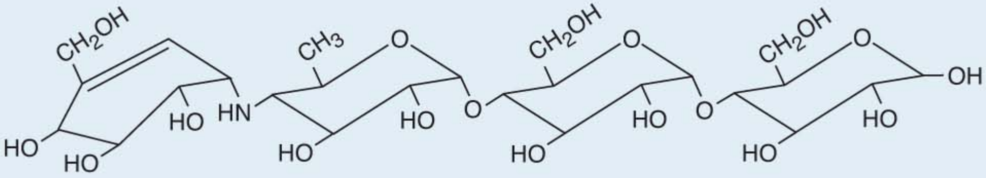
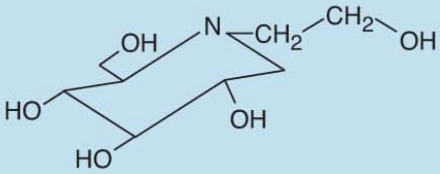
→可延緩 starch 及 disaccharide 之消化與吸收。

→∴降低餐後 glucose

p.743 Tab 41-9

Table 41-9.

TABLE 41–9 Alpha-glucosidase inhibitors.

Alpha-Glucosidase Inhibitor	Chemical Structure	Oral Dose
Acarbose (Precose)		25–100 mg before meals
Miglitol (Glyset)		25–100 mg before meals

五、 Others

1. Pramlintide :

◎本品是 amylin 合成物。

◎注射，用於調節飯後高血糖。

2. Ezenatide

◎本品是 glucagon-like polypeptide-1(GLP-1) 之合成物。

◎注射用於 type2

3. 3.Sitagliptin

◎本品是 dipeptidyl peptidase-4 (DPP-4) 之抑制劑

◎本品能增加 glucose-mediated insulin 分泌↑及降低 glucagon level ↓

→而降低飯後 glucose

◎口服 85%bioavailaility， 半衰期 12hr

五、 GLUCAGON

◎從 Pancreat α cell 所分泌

◎為 29 amino acid ， M.W.=3485

◎Glucagon-like peptide 1(GLP-1)

1. 藥理作用 ：

(1) Metabolic Effects :

→增加 cyclic AMP， 使貯存之 glucogen 加速代謝，及增加 glyconeogenesis ↑

∴血糖上升 (Glucagon 對骨骼肌 glycogen 不影響 ， 因骨骼肌上無 glycogen receptor)。

→Glucagon 使正常， β cell 分泌 insulin 以及使 :

<I> Pheochromcytoma 親鉻細胞瘤→分泌 Catecholamine

<Ⅱ>Medullary carcinoma cell → 分泌 Calcitonin

(2)Cardiac Effects :

加強心臟之 inotropic 及 chronotropic 但臨床上不能用於 HF

(3) Effect on Smooth Muscle :

∵大量 glucagon 使小腸平滑肌 relax

∴使用於 X-ray 以觀察常內臟

2.Clinical Uses :

(1)Severe hypoglycemia

主要用於 insulin dependent patient 發生嚴重性低血糖時，使用於急救 (∵ glucagon 能使血糖上升)

(2)Endocrine diagnosis

1 mg glucagon I.V.

正常人在 10 分內， Pancreatic C-peptide 達到標準濃度， 如 IDDM p’t 則無 c-peptide 反應。

(3) 增加新機的收縮力

可用來治療因 β-blocker 過量造成中毒。

六、 ISLET AMYLOID POLYPETIDE (IAPP , AMYLIN)

1. 37-amino-acid polypeptide 之有機衍生物
2. 來自 long-standing Type2 or insulinomas 病人 pancreas 之 islet amyloid deposits
3. produced by β cell

AGENTS THAT AFFECT BONE MINERAL HOMEOSTASIS

I. BASIC PHARMACOLOGY

→骨內主要之礦物質為 calcium 與 phospate

→calcium 與 phosthate 主要由腸胃道吸收

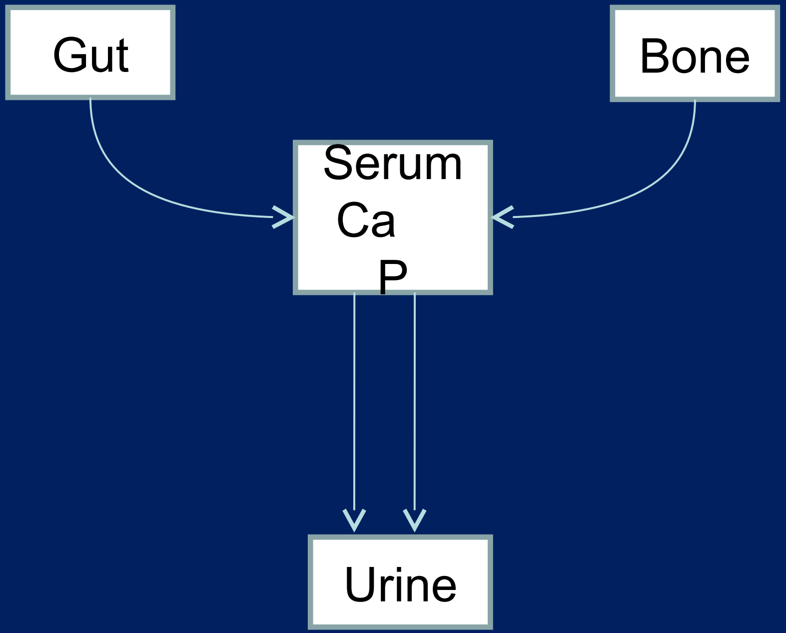
→調節 calcium 與 phosphate homeostasis 之 hormone

1.polypeptide parathyroid hormons (PTH)

2.steroid citamine D

3.others:calcitonin,prolactin,growth hormone,inauline , thyroid hormone,glucocorticoids ,

and sex steroid .



D(+)

D(+)
PTH(+)
CT(-)

D(-)
PTH(-)
CT(+)

D(-)
PTH(+)
CT(+)

Figure 42–1.

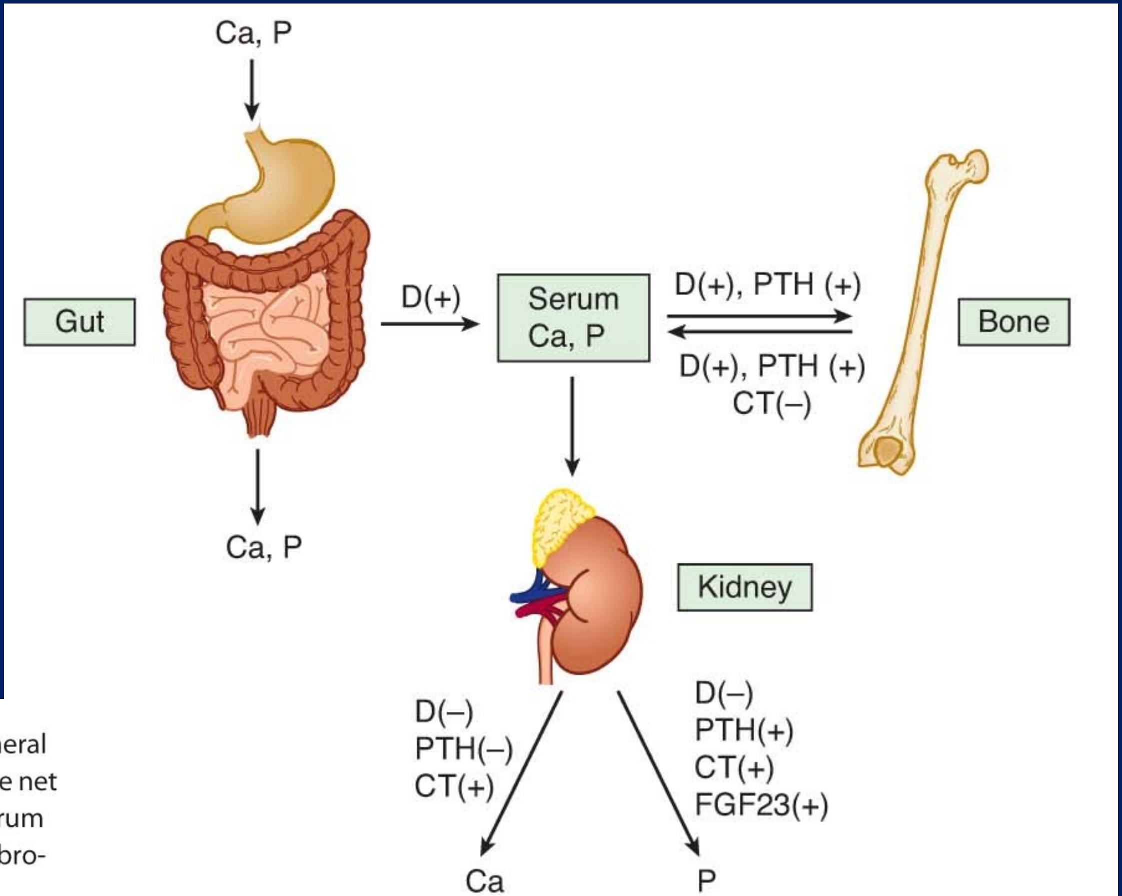


FIGURE 42–1 Some mechanisms contributing to bone mineral homeostasis. Direct actions are shown and feedback may alter the net effect. Calcium (Ca) and phosphorus (P) concentrations in the serum are controlled principally by three hormones, $1,25(OH)_2D_3$ (D), fibroblast growth factor 23 (FGF23), and parathyroid hormone (PTH), through their action on absorption from the gut and from bone and on excretion in the urine. PTH and $1,25(OH)_2D_3$ increase input of calcium and phosphorus from bone into the serum and stimulate bone formation. $1,25(OH)_2D_3$ also increases calcium and phosphate absorption from the gut. $1,25(OH)_2D_3$ decreases urinary excretion of both calcium and phosphorus, whereas PTH reduces calcium but increases phosphorus excretion. FGF23 stimulates renal excretion of phosphate. Calcitonin (CT) is a less critical hormone for calcium homeostasis, but in pharmacologic concentrations can reduce serum calcium and phosphorus by inhibiting bone resorption and stimulating their renal excretion. Feedback may alter the effects shown; for example, vitamin D usually increases urinary calcium excretion because of effects on calcium absorption from the gut and effects on PTH.

◆Principal Hormonal Regulators Bone Mineral Homeostasis :

1. 骨、 礦物質平衡之主要荷爾蒙調節劑 :

<1>.PTH : 84 氨基酸 ， 刺激 1,25$(OH)_2$D 形成

<2>.Vit D : 為 prohrmone ， 接受紫外光，由皮膚製造。

	PTH	Vit D
小腸	增加鈣、磷吸收↑	增加鈣、磷吸收
腎	減少鈣排泄↓ 增加磷排泄↑	減少鈣、磷排泄
骨	於高劑量增加鈣、磷吸收於低劑量增加骨骼形成	增加鈣、磷吸收
血中淨值	鈣↑ 磷↓	鈣↑ 磷↑

◎Vit D

Vit D2 (Ergocalciferol) → 經肝 hydroxylate 才有效。

Vit D3 (Cholecalciferol)→ 經肝 hydroxylate 才有效。

※臨床上常用 : 25(OH) D_3 : Calcifediol

1,25$(OH)_2$ D_3 : Calcitriol (t1/2 : 1-3 days)

p.757 fig42-2 p756 fig 42-3

Figure 42–2.

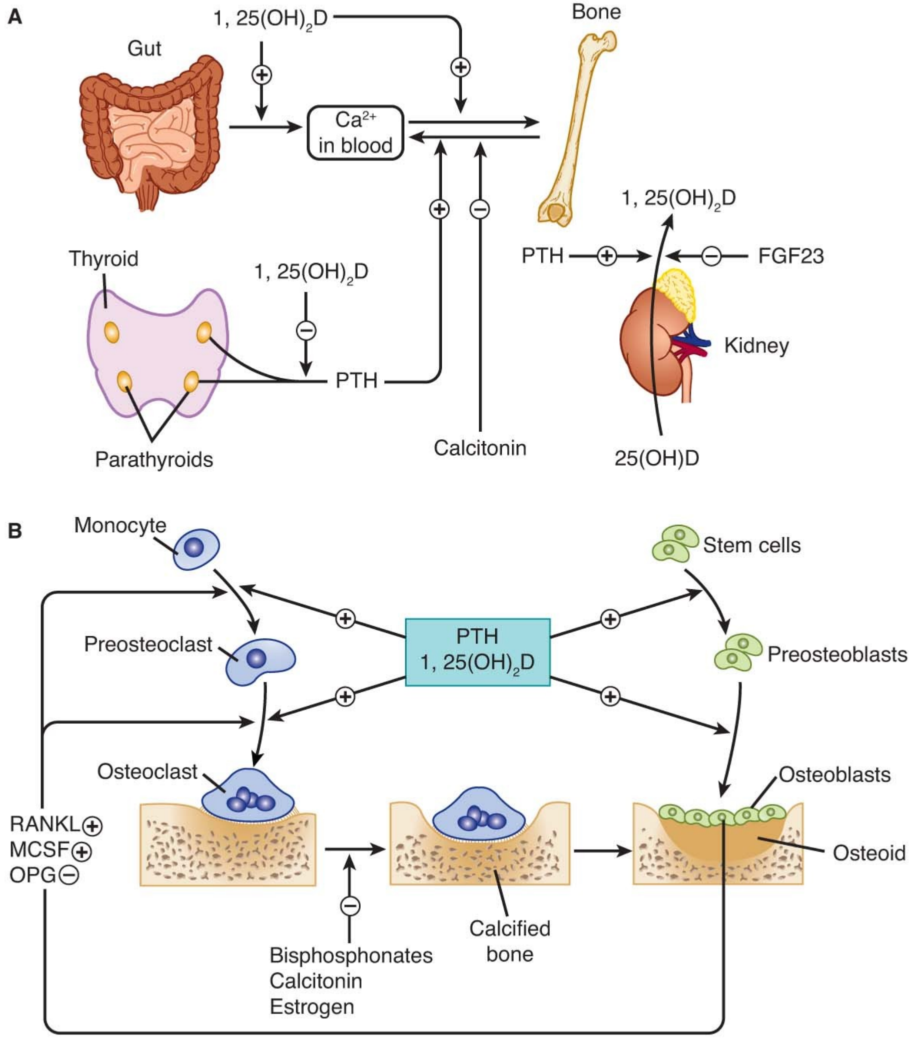


FIGURE 42–2 The hormonal interactions controlling bone mineral homeostasis. In the body (**A**), $1,25(OH)_2D$ is produced by the kidney under the control of parathyroid hormone (PTH), which stimulates its production, and fibroblast growth factor 23 (FGF23), which inhibits its production. $1,25(OH)_2D$ in turn inhibits the production of PTH by the parathyroid glands and stimulates FGF23 release from bone. $1,25(OH)_2D$ is the principal regulator of intestinal calcium and phosphate absorption. At the level of the bone (**B**), both PTH and $1,25(OH)_2D$ regulate bone formation and resorption, with each capable of stimulating both processes. This is accomplished by their stimulation of preosteoblast proliferation and differentiation into osteoblasts, the bone forming cell. PTH and $1,25(OH)_2D$ stimulate the expression of RANKL by the osteoblast, which, with MCSF, stimulates the differentiation and subsequent activation of osteoclasts, the bone resorbing cell. FGF23 in excess leads to osteomalacia by inhibiting $1,25(OH)_2D_3$ production and lowering phosphate levels. MCSF, macrophage colony-stimulating factor; OPG, osteoprotegerin; RANKL, ligand for receptor for activation of nuclear factor-κB.

Figure 42–3.

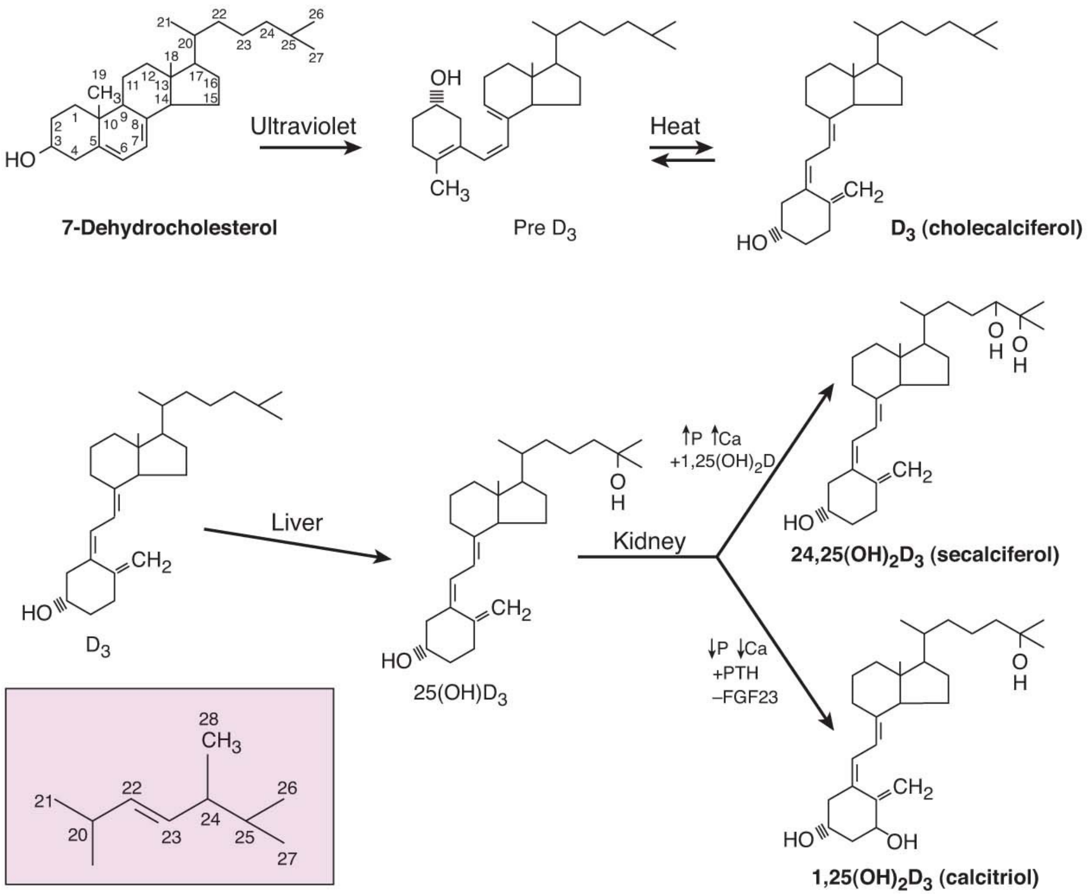


FIGURE 42–3 Conversion of 7-dehydrocholesterol to vitamin D_3 and metabolism of D_3 to $1,25(OH)_2D_3$ and $24,25(OH)_2D_3$. Control of the latter step is exerted primarily at the level of the kidney, where low serum phosphorus, low serum calcium, and high parathyroid hormone favor the production of $1,25(OH)_2D_3$, whereas fibroblast growth factor 23 inhibits its production. The inset shows the side chain for ergosterol. Ergosterol undergoes similar transformation to vitamin D_2 (ergocalciferol), which, in turn, is metabolized to $25(OH)D_2$, $1,25(OH)_2D_2$, and $24,25(OH)_2D_2$. In humans, corresponding D_2 and D_3 derivatives have equivalent effects and potency. They are therefore referred to in the text without a subscript.

- Fibroblast Growth factor 23

→FGF23 是 single-chain protein 有 251 amins acids

→它抑制腎臟 1,25 (OH)2D3 產生及磷再吸收

(經由 sodiam phosphate co-transporters Napi2aQ2c)

→因此產生 hypophosatemia 及降低 1,25 (OH)2D3 在血中濃度。

◆Interaction of PTH , FGF 23 , and vitamin D

1.1,25(OH)2D→ 抑制 PTH 分泌

2.chronic kidney disease 因血磷過高→ secondary hyperparathroidism

3. 洗腎病人因血磷高↑

∴要洗腎將血磷降下。

4.calcitriol 也可用於 primary byperparathyroidism

5.1,25(OH)2D3→ 刺激 FGF 23 產生↑

6.FGF23→ 抑制 1,25(OH)2D3 production

7. 但當 hypohosphatemia , negative feedback:1,25(OH)2D3 則抑制 FGF23 production

p.758 Tab42-2

Table 42-2.

TABLE 42–2 Actions of parathyroid hormone (PTH), vitamin D, and FGF23 on gut, bone, and kidney.

	PTH	Vitamin D	FGF23
Intestine	Increased calcium and phosphate absorption (by increased $1,25[OH]_2D$ production)	Increased calcium and phosphate absorption by $1,25\ (OH)_2D$	Decreased calcium and phosphate absorption by decreased $1,25(OH)_2$ production
Kidney	Decreased calcium excretion, increased phosphate excretion	Calcium and phosphate excretion may be decreased by 25(OH)D and $1,25(OH)_2D$[1]	Increased phosphate excretion
Bone	Calcium and phosphate resorption increased by high doses. Low doses may increase bone formation.	Increased calcium and phosphate resorption by $1,25(OH)_2D$; bone formation may be increased by $1,25(OH)_2D$ and $24,25(OH)_2D$	Decreased mineralization due to hypophosphatemia
Net effect on serum levels	Serum calcium increased, serum phosphate decreased	Serum calcium and phosphate both increased	Decreased serum phosphate

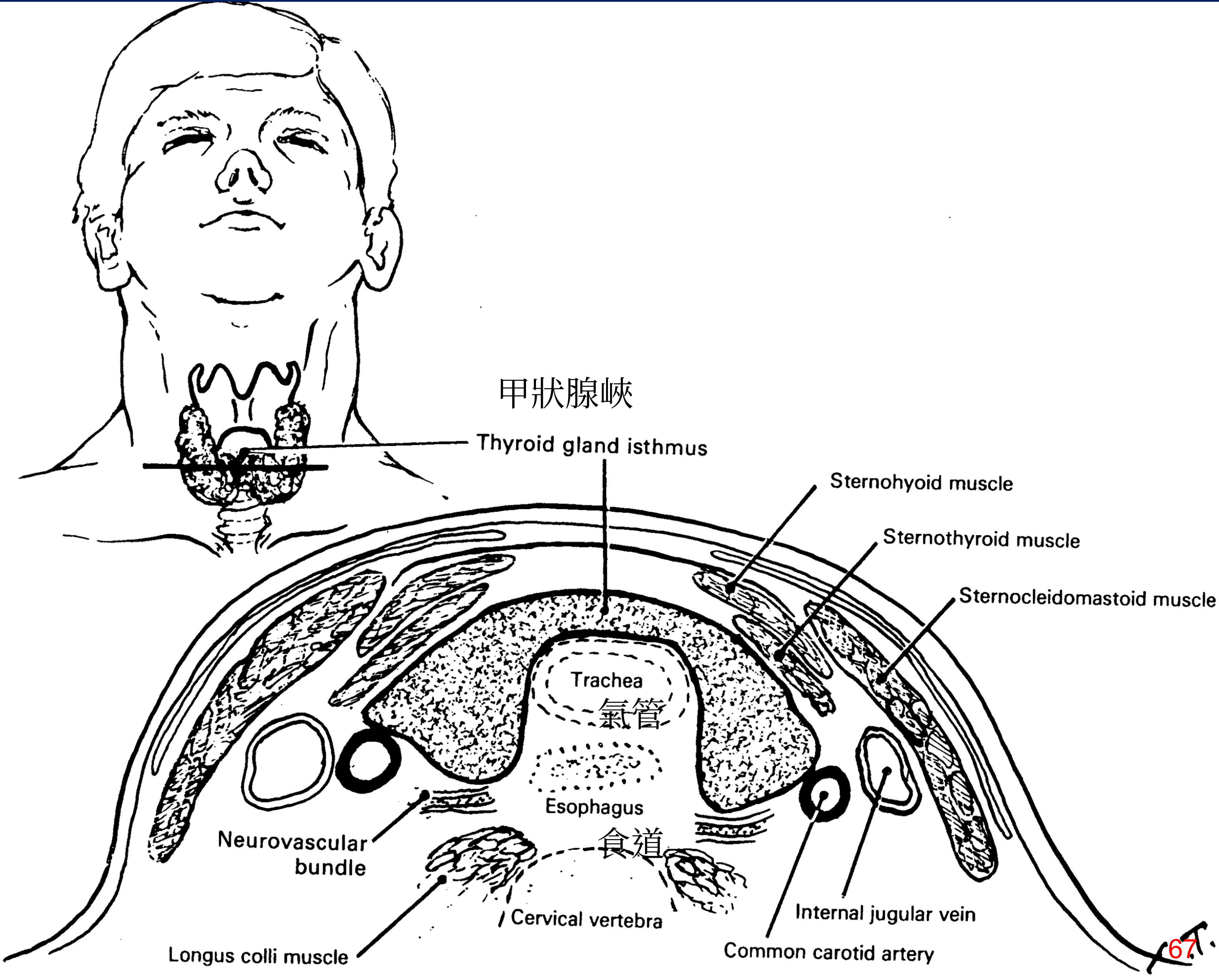
[1]Direct effect. Vitamin D often increases urine calcium owing to increased calcium absorption from the intestine and resulting decreased PTH.

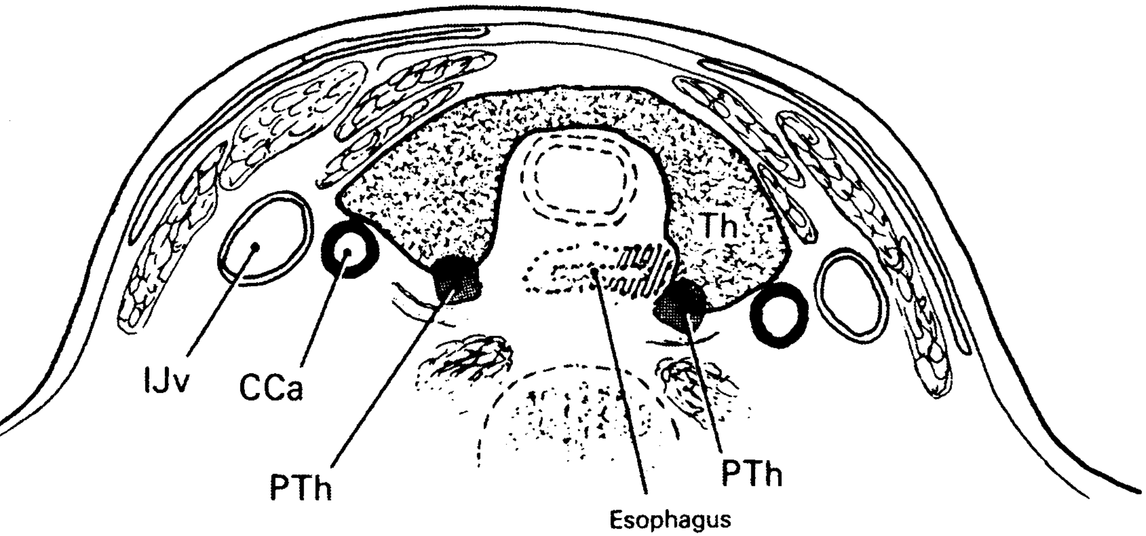
尿毒症患者副甲狀腺瘤之治療

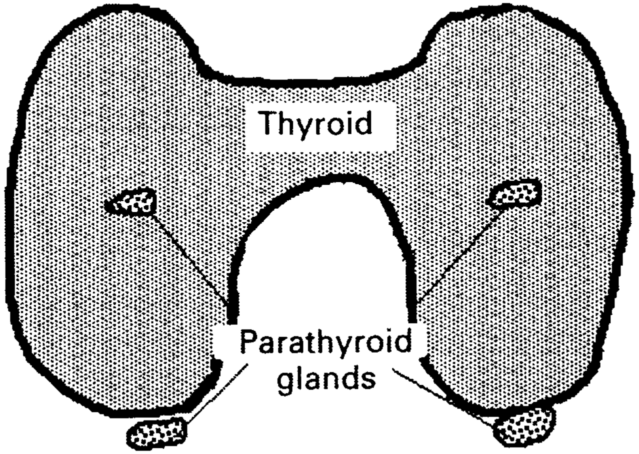
陳嘉聖 醫師

中國醫藥學院附設醫院 內科部腎臟科

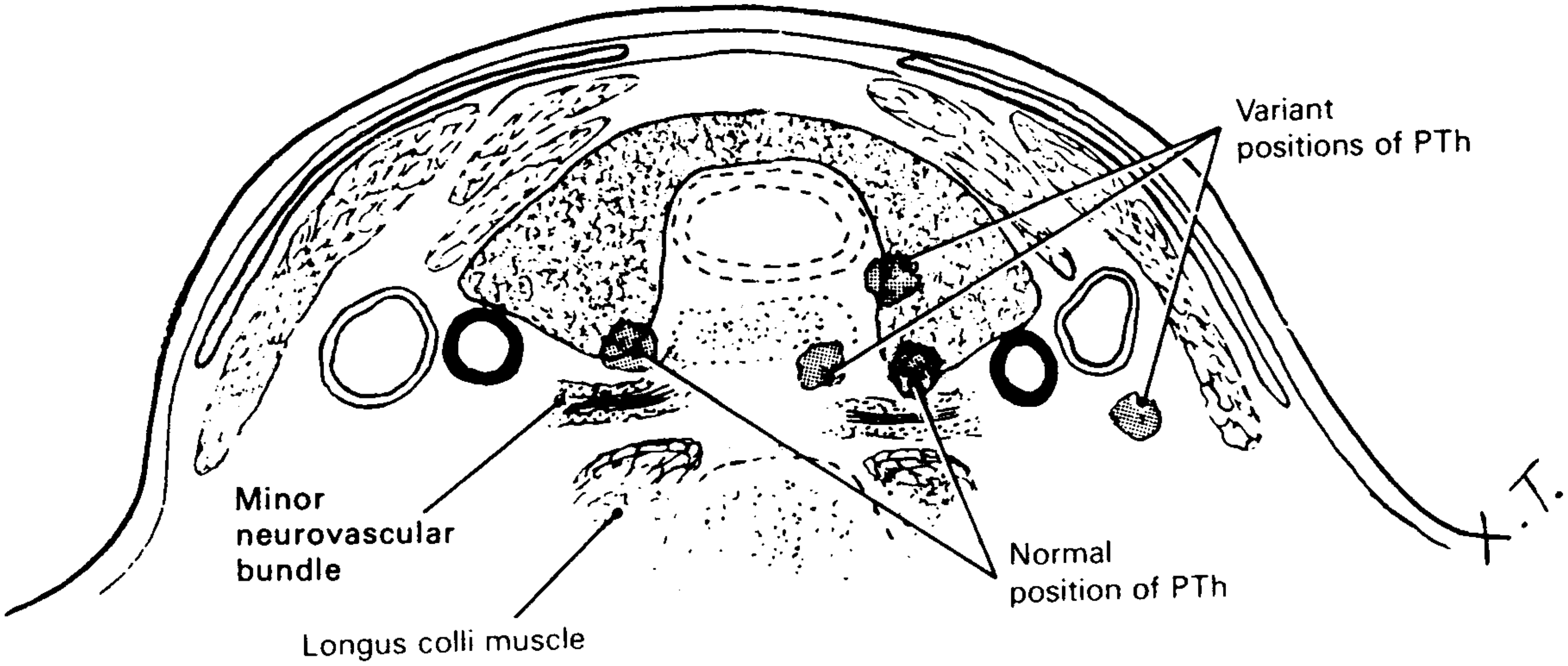
The Anatomy of Parathyroid Gland


甲狀腺峽
Thyroid gland isthmus
Sternohyoid muscle
Sternothyroid muscle
Sternocleidomastoid muscle
Trachea
氣管
Esophagus
食道
Neurovascular bundle
Cervical vertebra
Longus colli muscle
Internal jugular vein
Common carotid artery





B

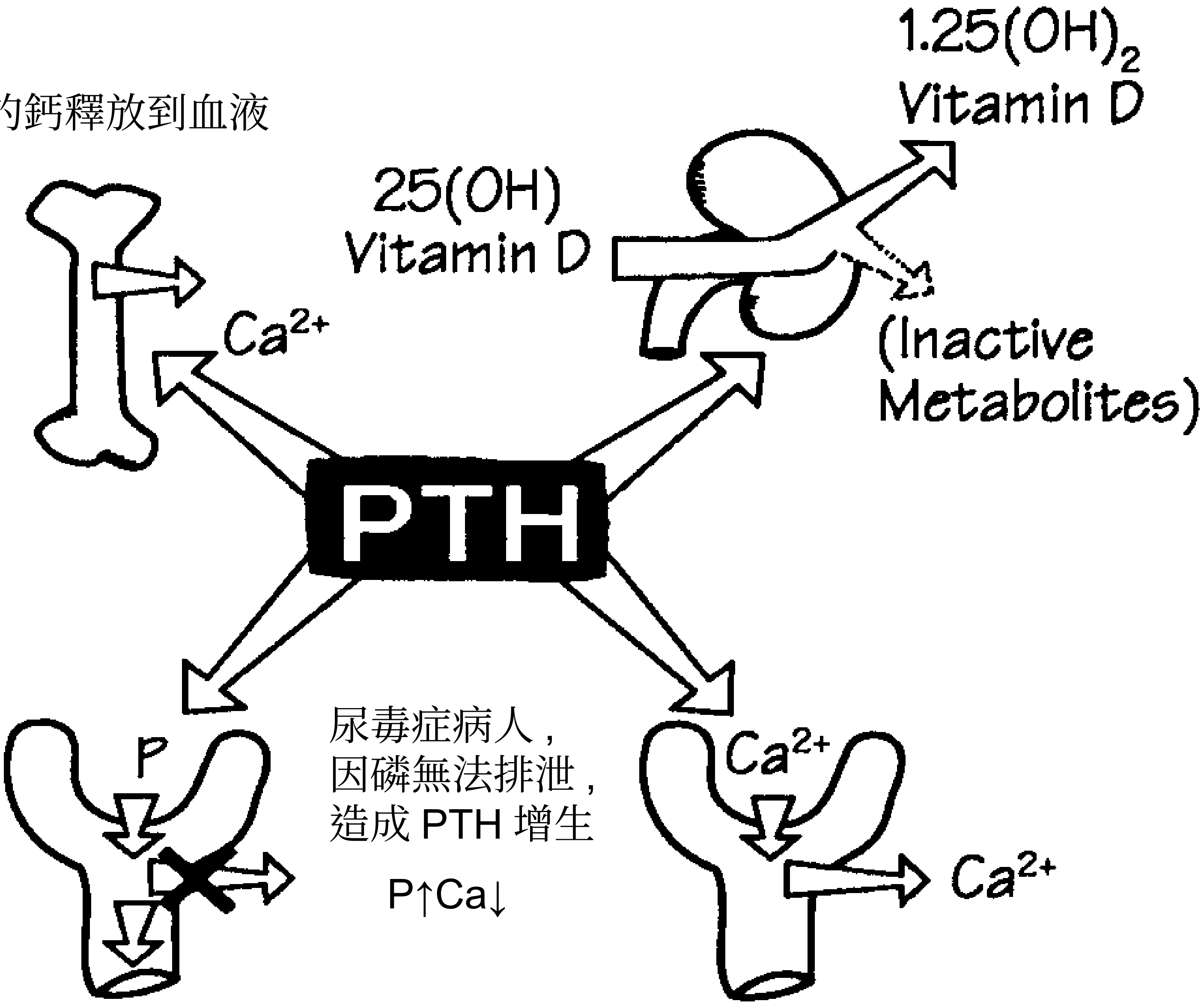

Variant
positions of PTh
Minor
neurovascular
bundle
Normal
position of PTh
Longus colli muscle
X.T.

Physiology of Parathyroid Hormone

- PTH is an 84 amino acid polypeptide secreted from the parathyroid glands in response to low levels of ionized Ca in the extra-cellular fluid.
- Increasing circulation of PTH lead to

1. Mobilization of Ca from bone
2. Enhancement of Ca reabsorption in the renal tubule
3. Increased production of $1,25(OH)_2D_3$ by proximal tubule cells

把骨頭的鈣釋放到血液



尿毒症病人，
因磷無法排泄，
造成 PTH 增生

P↑Ca↓

增加腎磷的排泄

促進腎鈣的再吸收

Metabolism of Vitamin D

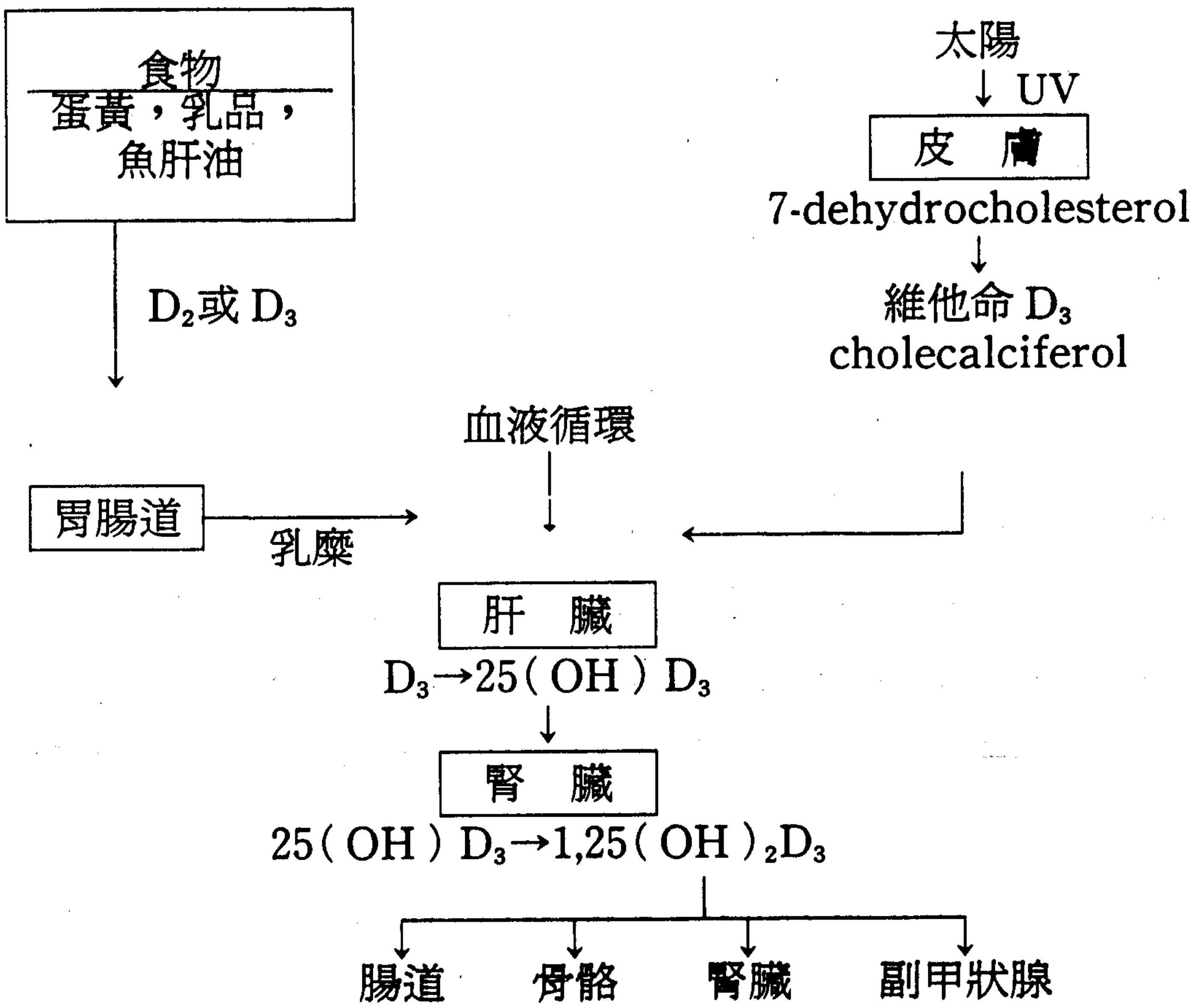


圖27-2維他命 D 之代謝與功能

Uremia affects the metabolism of

1. Parathyroid gland

   (1) decreased the metabolism of parathyroid gland (when CCr < 30%)

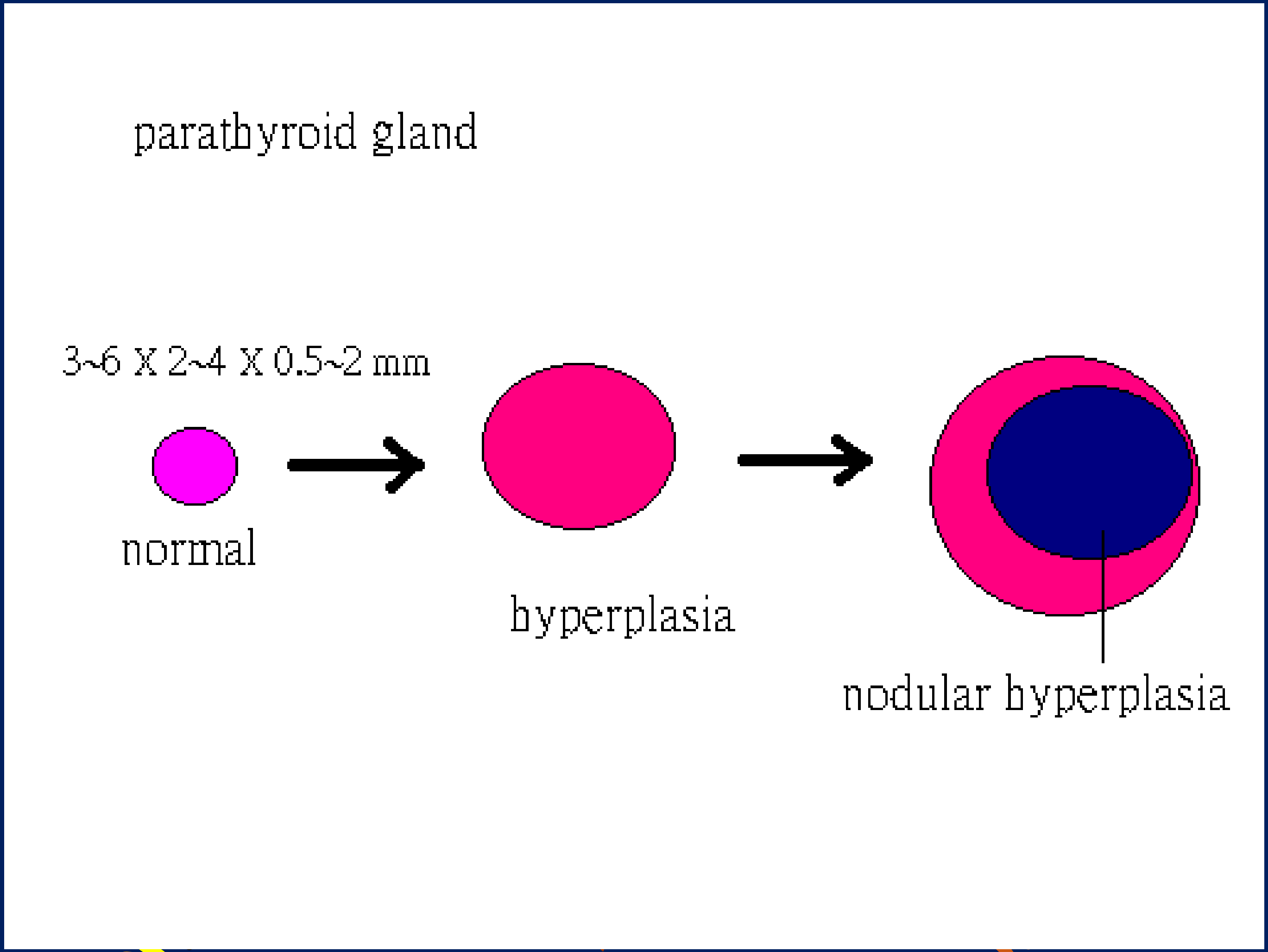
   (2) increased the secretion of parathyroid gland

2. Decreased $1,25(OH)_2D_3$ – Phosphate retention, inhibit the 1 –hydroxylase directly

The pathogenesis of 2nd hyperparathyroidism (SHP) in uremia

1. Hypocalcemia
2. Phosphate retention—was the most important factor (Salem *Am J Kidney Dis* 1997; 29(6): 862-5)
3. Decreased $1,25(OH)_2D_3$
4. Resistance of bone to PTH
5. Abnormal set point of Ca

Cell biology of parathyroid hyperplasia in uremia



Treatment of 2nd hyperparathyroidism

1. Control of serum phosphorus levels (kept 4.5~5.5 mg/dl): $CaCO_3$, $Al(OH)_3$..
2. Prevention of hypocalcemia (kept 9.5~11.0 mg/dl): $CaCO_3$
3. Vitamin D supplement: IV calcitriol, po alfacalcidol

Recent developments in the management of SHP

1. Control serum phosphate: Sevelamer hydrochloride (RenaGel[R])
2. Vitamin D : paricalcitol(降 PTH, 但比較不會升 Ca, P)…
3. Calcimimetic agents: modify signal transduction by CaSR (directly activating the CaSR, reduction in PTH release)—R568

But if medical therapy is failure..

Persistent high level of iPTH or S/S
of high turn over bone disease
(腎骨病變)

Secondary Hormonal Regulators of Mineral Homeostasis

(1)Calcitonin 亦鈣激素 :

使用於 Paget’s 及血鈣過高症

→本品由甲狀腺 Parafolicular cell 分泌，臨床所用者為鮭魚 Salmon calcitonin

→本品作用於胃、腎，使血中鈣、磷均↓

(2)Glucocorticoids :

使用於 hypercalcemia

cortisol 結抗 Vit D 刺激小腸鈣之 transport

由於抑制骨 collagen 之合成 → 造成骨鬆症。

(3)Estrogens :

本品可預防停經後骨鬆症

本品可增加血中 $1,25(OH)_2D$ 濃度↑

Nonhormonal Agents Affecting Bone Mineral Homeostasis

(1)Diphosphonates：代表性藥　Etidronate

抑制　1,25$(OH)_2$D 之　production

抑制小腸內鈣之 transoprt

(2)Mithramycin (Plicamycin)

治療血鈣過高症，　Paget’s disease (變形性骨炎　Osteitis deformans)

(3)Thiazides :

減少腎之鈣排泄

減少血鈣過高所引起之結石症

∵本品能減少尿中草酸排泄，但能增加尿中鎂、 Zinc level ，　此二者能抑制草酸鈣之

形成

(4)Fluoride :

可用於鬆骨症新股之形成

防蛀牙 dental caries 水中含　0.5~1ppm

急性中毒　：心血管　collapse ，　呼吸衰竭

慢性爆露於氟空氣中，　會 Croppling Fluorosis　〔骨贅 (椎骨) 長骨加粗〕殘廢

(5)Calcimimetics :

- Cinacalcet : 活化 calcium sensing rtceptor (Ca R)
- 本品 block PTH secretion

→治療 secondary hyperparathyroidism (in chronic kidney disease)

→治療 parathyroid carcinoma

(6) Strontium Ranelate :

- 本品是由一個 organicion , ranelic acid 和兩個 strontium 原子所結合
- U.S.A 未核准使用
- 本品 block 骨細胞分化。促進 bone formation

Ⅱ.CLINICAL PHARMACOLOGY

一 .Abnormal Serum Calcium & Phospate Levels

1.Hypercalcemia : (與 thiazide 引起者不同)

主由於 hyperparathyroidism ，骨癌 ；及次由於 hypervitaminosis D ，類肉瘤 Sarcoidosis ，thyrotoxicosis …… 等引起。

【治療】 :

(a)Saline diuresis (rehydration)

furosemide(diuresis)

(b)Calcitonin-Salmon(Calcimar)

100IU/ml for inj .

Ⅱ.CLINICAL PHARMACOLOGY

一 .Abnormal Serum Calcium & Phospate Levels

【治療】：

(c)Mithramycin：以上藥物無效時，採用之 25~50 g/Kg

(d) 以上無效時，使用之緩慢給藥

* 對於急性血鈣過高，藥效不明，但對於慢性骨癌，可使用之。

2.Hypocalcemia :

- 特徵：感覺倒錯
- 主要原因係由副甲狀過低症 缺乏 腎衰竭 吸收不良

成人　：

(1)Calcium gluconate 0.45 mEq/ml. I.V.

(2)Vit D:1,25$(OH)_2D_3$(Calcitriol) 每天 0.25-1 μg

3.Hyperphosphatemia :

- 腎衰竭之併發症，亦可由 hypoparathyroidism 發現之，及 Vit D intoxication 。
- 骨癌治療用 dialysis , glucose 及 insulin infusion 病要限制食物中含磷，及使用 $Al(OH)_3$ gel 補充鈣。

4. Hypophosphatemia

- 由下列因素所發生：

  副甲狀過高↑

  Vit D 缺乏

  腎大量排出磷 (fanconi's syndrome) 。

  過量使用 $Al(OH)_3$ gel

- 臨床上少見，肌無力，軟骨病，
- 治療給予 phosphate (Fleet phospho-Sida: 含 815 mg phosphate , 760mg Sod./5 ml)

二 .Specifie Disoders Involving The Bone Mineral Regulating Hormones

1.Primary Hyperparathyroidism

外科手術

2.Hypoparathyroidism

- PTH 血鈣↑，血磷↓ (正常功能)
- 血鈣↓，血磷↑ (PTH 低者)
- 給予 Vit D 二萬五 ~ 十萬丹為每周 3 次、口服或給 calcitriol

3.Nutritional Rickets 拘僂病

食物中缺 Vit D 或減少陽光

每天給 400 單位 Vit D

4.Chronic Renal Failure

→不能製造 1,25 $(OH)_2D$， 24,25$(OH)_2D$

→滯留 phosphate → 會降低鈣離子的濃度

→ 使用 calcitriol 〔1,25 $(OH)_2D_3$〕

5.Intestinal Osteodystrophy 骨發育不全

- 由於、胃、肝疾病所造成，為鬆骨症，及軟骨病 (osteomalacia) ，鈣、口吸收不良。
- 使用 calcitriol ， calcifediol 。

6.Osteoporosis (即不正常缺骨，易骨折)

- 易發生於 : 停經婦女

  老年人

  長期服用 cortisol , Alc , abuse ….
- 婦女用 estrogen
- 男人給 Vit D

7. Vit D – resistant Rickets (拘僂)

由於 renal phosphate 再吸收不正常引起

8. Vit D – dependent Rickets

(1)Type I

由於缺乏 1,25 $(OH)_2D$ production，

治療用 Vit D 4 千單位每天，或 Calcitrol 0.25 – 0.5 μg 每天

(2)Type II

對於 1,25 $(OH)_2D$ 之作用無反應，血中之 1,25 $(OH)_2D$ 高

9.Nephrotic Syndrome

- Vit D 是 Prohormone，

於肝 hydroxylation →25 hydroxy Vit D

→25 (OH)D

再於腎轉換成 1,25 dihydroxy Vit D

1,25 (OH)2D

及 24,25-dihydroxy Vit D

24,25 (OH)2D

- 臨床使用：

25(OH)D Calcifediol

1,25 (OH)2D Calcitriol

- α – globulin

  與 25(OH)2D ,24,25(OH)2D 結合力強

  與 Vit D (cholecalciferol) , 1,25 (OH)2D 結合力弱

- Neprotic syndrome

  喪失 Vit D - binding protein 之能力

  ∴25(OH)D level↓

10.Idiopathic (特發性)Hypercalciuria

(I) 腸過度吸收鈣，使血鈣↑

制 PTH ↑

∴.Secondary 增加尿中鈣。

(Ⅱ)Renal calcium leaker 漏出

(Ⅲ) 病人 primary 減低 phosphate 再吸收

使 1,25 $(OH)_2D$ production ↑,

增加腸鈣吸收 ；使血鈣↑，降低 PTH↓

∴ Secondary 增加 urine calcium

※ 治療可使用 thiazide , 因它之副作用為 hypokalemis , hyperglycemia 及 hypercalcemia 。

三、 Other Disorders of Mineral Homeostasis

※Paget's disease

係變形骨炎 ：

長骨發現腫脹變形，長度不等，而發生步態異常；顱骨擴大，帽子愈緊 ；臉痛 ，頭痛 ；high-output cardiac failure

【治療】：

(I) 可使用 calcitonin 50~10MRC 單位 s.c.

(British Medical Research Council)

(Ⅱ)Sod. Etidronate 5 mg/ μg，每天 P.O.

(diphosponates，抑制 1,25 $(OH)_2D$ 之產生)

※ Enteric Oxaluria

- 病人有脂肪吸收異常 (fat malabsorption) 之 short bowel syndrome

  →可能會有鈣和 oxala 結石

- 尿中 oxalate 濃度高↑

- 每天分開給予 1-2 g calcium carbonate 但要小心監控尿中 oxalate 有下降，但尿中鈣不會增加。